Clinical Neurophysiology 129 (2018) 2290–2295

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Sudomotor dysfunction is frequent and correlates with disability in Friedreich ataxia

Karen A.G. Takazaki [a], Thiago Junqueira R. Rezende [a], Alberto R.M. Martinez [a], Carelis Gonzalez-Salazar [a], Anamarli Nucci [a], Iscia Lopes-Cendes [b], Marcondes C. França Jr. [a,*]

[a] Departments of Neurology, School of Medical Sciences, University of Campinas – UNICAMP, Campinas, SP, Brazil
[b] Medical Genetics, School of Medical Sciences, University of Campinas – UNICAMP, Campinas, SP, Brazil

ARTICLE INFO

Article history:
Accepted 22 August 2018
Available online 31 August 2018

Keywords:
Friedreich's ataxia
Autonomic nervous system
Heart rate variability
Sudomotor function
QSART

HIGHLIGHTS

- Cardiovascular dysautonomia is not common in Friedreich's ataxia (FRDA).
- Sudomotor dysfunction is frequent and related to peripheral damage in FRDA.
- QSART correlates with ataxia severity and is a promising biomarker for FRDA.

ABSTRACT

Objectives: To evaluate autonomic symptoms and function in Friedreich's Ataxia (FRDA).
Methods: Twenty-eight FRDA patients and 24 controls underwent clinical/electrophysiological testing. We employed the Friedreich's Ataxia Rating Scale (FARS) and the Scales for Outcomes in Parkinson's Disease: Autonomic Questionnaire-SCOPA-AUT to estimate the intensity of ataxia and autonomic complaints, respectively. Cardiovagal tests and the quantitative sudomotor axonal reflex, Q-SART, were then assessed in both groups.
Results: In the patient group, there were 11 men with mean age of 31.5 ± 11.1 years. Mean SCOPA-AUT score was 15.1 ± 8.1. Minimum RR interval at rest was shorter in the FRDA group (Median 831.3 × 724.0 ms, $p < 0.001$). The 30:15 ratio, Valsalva index, E:I ratio, low and high frequency power presented no differences between patients and controls ($p > 0.05$). Sweat responses were significantly reduced in patients for all sites tested (forearm 0.389 × 1.309 μL; proximal leg 0.406 × 1.107 μL; distal leg 0.491 × 1.232 μL; foot 0.265 × 0.708 μL; p value < 0.05). Sweat volumes correlated with FARS scores.
Conclusions: We found abnormal sudomotor but normal heart rate variability in FRDA. Small cholinergic post-ganglionic fibers are affected in the disease.
Significance: Quantification of sudomotor function might be a biomarker for FRDA.

1. Introduction

Friedreich ataxia (FRDA) is considered the most prevalent autosomal recessive ataxia worldwide with estimated prevalence of 3/100,000. The disease is common in Caucasian populations, but practically absent in sub-saharan regions and in the Far East. In 95% of the cases, the underlying cause is a homozygous expansion of a (GAA) repeat in intron 1 of *FXN* at 9q21.1 (Koeppen, 2011; Durr et al., 1996; Campuzano et al., 1996; Fogel and Perlman, 2007). This leads to a transcriptional abnormality that results in the lack of frataxin, a mitochondrial protein related to iron homeostasis (Campuzano et al., 1997). Neurological signs include ataxia, dysar-

Abbreviations: FRDA, Friedreichs's ataxia; FARS, Friedreich's Ataxia Rating Scale; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease – Autonomic Questionnaire; HRV, heart rate variability; E:I ratio, expiratory, inspiratory ratio; LF, low frequency band; HF, high frequency band; R30, maximum-to-minimum variation in deep breathing; QSART, quantitative sudomotor axonal reflex test; LFPA, low frequency power; HFPA, high frequency power; MIBG, meta-iodo benzylguanidine.

* Corresponding author at: Department of Neurology, University of Campinas – UNICAMP, Rua Tessália Vieira de Camargo, 126, Cidade Universitaria "Zeferino Vaz", Campinas, SP 13083-887, Brazil.
E-mail address: mcfrancajr@uol.com.br (M.C. França).

https://doi.org/10.1016/j.clinph.2018.08.017
1388-2457/

thria, lower limb atrophy and weakness, widespread areflexia, Babinski sign, loss of joint and vibratory sensation, and sensory neuronopathy. Other clinical features that may be present are scoliosis, feet deformities (*pes cavus*), diabetes and cardiomyopathy (Koeppen, 2011; Pandolfo, 2008).

Autonomic dysfunction is present in several neurodegenerative disorders, including some inherited ataxias such as SCA3 (Takazaki et al., 2013; Yeh et al., 2005, França et al., 2010, Pradhan et al., 2008, Netravathi et al., 2009). Despite that, very few studies looked specifically at autonomic function in patients with FRDA. These included small cohorts and analyses were restricted to cardiovagal parameters (Ingall et al., 1991, Pousset et al., 1996). Moreover, most of them were published before the causal mutation of FRDA was identified, raising concerns about the diagnostic accuracy (Durr et al., 1996). Sudomotor function has never been properly explored in FRDA. Therefore, it remains unclear the real frequency and clinical relevance of dysautonomic manifestations in the disease.

Therefore, we believe that autonomic function deserves investigation in the disease. To accomplish that, we recruited a representative cohort to undergo detailed clinical and neurophysiological evaluation, using established techniques (Task force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996; Ravits, 1997; Low et al., 2006). We attempted to determine the frequency and the intensity of autonomic manifestations in patients with FRDA, using quantitative methods. We hypothesized that sudomotor and cardiovascular autonomic function would be abnormal in patients with FRDA. Furthermore, these abnormalities would correlate with other measures of disease status, such as duration and ataxia severity.

2. Methods

2.1. Subjects' selection

We first recruited 40 patients older than 18 years with genetic confirmation of homozygous abnormal (GAA) expansions at *FXN*. All of them were regularly followed at the University of Campinas hospital. These individuals were recruited between August/2015 and September/2017.

Most patients were taking Coenzyme Q10 and other vitamins ($n = 25/28$). We excluded 5 patients who used drugs known to interfere with autonomic function such as α and β blockers, β agonists, tricyclic antidepressants, α-metildopa, anti-histamines, diuretics and fludrocortisone. Seven diabetic patients were also excluded from further analyses. So, we were left with 28 patients for further clinical and neurophysiological analyses.

We recruited 24 healthy controls with similar age and gender distribution as in the FRDA group. None had neurological complaints. All of them had normal clinical and neurological examination. They were mostly students at the University of Campinas and volunteers from the local community. They were enrolled between 2015 and 2017. We took into account the same exclusion criteria employed for the FRDA group (described above).

This study was approved by our IRB (comitê de ética em pesquisa da UNICAMP). Each participant signed a written informed consent before any study-related procedure.

2.2. Clinical evaluation

All patients underwent clinical and neurological evaluation. Severity of ataxia and autonomic symptoms were quantified using the Friedreich's ataxia rating scale – FARS (Sudarsky, 2007) and the Scales for Outcomes in Parkinson's Disease – Autonomic Questionnaire (SCOPA – AUT, Carod-Artal et al., 2010), respectively. The last questionnaire was chosen because it is the only validated autonomic scale for Brazilian Portuguese. Moreover, it has been successfully employed in studies that assessed autonomic features in inherited ataxias, including a recently published report on FRDA (Takazaki et al., 2013; Indelicato et al., 2018). We also measured blood pressure (BP) and heart rate in supine and orthostatic positions.

2.3. Heart rate variability (HRV) analyses

2.3.1. Procedure

We performed neurophysiological tests in the morning using the WR medical HRV testing lab and the Nihon Kohden autonomic software running on the MEB 9200J electromyographer. All subjects were instructed to refrain from taking alcohol, coffee or nicotin in the 12 h before testing. All procedures took place in a quiet and temperature-controlled room (23–26 °C). We asked patients and controls to lay supine for 5 min prior to the onset of the tests.

We assessed HRV using a D2 derivation of the conventional electrocardiogram (bandpass; 1–20 Hz, no filtering). Consecutive QRS complexes were recorded and the exact interval (in ms) between two successive complexes (RR interval) was then computed. We looked carefully all RR intervals to remove artifacts and ectopic beats visually.

HRV was first studied at rest (for 5 min); then in standing position for 3 min, during and after the Valsalva maneuver and finally during deep breathing (6 incursions per minute). Valsalva maneuver was performed with the patient in supine position, and head elevated at 30°. Patients were asked to blow a mouthpiece connected to a manometer, under 40 mm Hg pressure for 15 s. RR intervals were recorded during the maneuver and 45 s later. This procedure was repeated other 2 times, and the greater Valsalva index was used.

2.3.2. Time domain analyses

We have calculated, for each subject, 30:15 ratio, Valsalva index and Expiratory: Inspiratory (E:I) ratio, according to Ewing et al. (1980). We also determined minimum, maximum and mean RR interval at rest.

2.3.3. Frequency domain analysis (spectral power)

We performed spectral analyses from RR intervals obtained in a 5-min resting period. Fast Fourier transformation algorithm was used to switch time domain (ms) into frequency domain (Hz) data (Asahina et al., 2010). Then spectral power of the low (LF: 0.04–0.15 Hz) and high frequency bands (HF: 0.15–0.50 Hz) were determined, according to Asahina et al. (2010).

2.3.4. Definition of cardiac dysautonomia

We defined cardiac autonomic dysfunction according to the modified Ewing criteria (Ewing et al.,1980). Afterwards, patients were classified as having or not definite cardiac dysautonomia.

2.4. Quantitative sudomotor axonal reflex test (QSART)

Sudomotor function was assessed through QSART performed with the WR medical Q-SWEAT quantitative sweat measurement lab. Stimulus and recording were done through a multicompartmental sweat capsule, placed on standardized places for the test: forearm, proximal leg, distal leg and foot, on the left side. The capsule lays in the skin and its external ring is filled with acetylcholine 10% in solution. Internally, nitrogen gas flows over the skin and humidity outflow is measured by a hygrometer. When the baseline becomes stable, iontophoresis starts with acetylcholine at 2 mA for 5 min. Humidity is constantly measured up to 15 min after the stimulus onset. Volume of induced sweat is